CERHR Concept: State-of-the-Science Evaluation on Environmental Exposures and Diabetes and Obesity

Project Leader:
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Nomination Background and Rationale:
Recently, there has been increasing interest in the notion that environmental exposures may be associated with diabetes and obesity (Grun and Blumberg 2007; Boberg et al. 2008; Chen et al. 2009; Newbold et al. 2009), including recent coverage in Newsweek magazine.[1] In particular, exposures that occur early in life have been hypothesized to "program" the individual to have an increased risk of developing diabetes or becoming obese, for example, by altering aspects of glycemic control or adipocyte differentiation. The association between environmental contaminants and diabetes or obesity is an emerging topic in the field of environmental health sciences. Most of the published studies related to these health effects involve substances with widespread human exposure in the general population including: polychlorinated biphenyls (PCBs), perfluoroalkyl acids (PFAAs), arsenic, bisphenol A (BPA), and heavy metals such as cadmium. Although the scope and focus of the scientific literature varies from chemical to chemical, a large body of research is rapidly being developed on this issue for a range of chemicals. Many of these studies have only recently been published. For example, over half of the eighty relevant studies identified for arsenic have been published since 2006. Thus, the literature on these health effects is in a rapid phase of development and includes a relatively large number of human studies for certain exposures as well as a diverse range of animal and *in vitro* model systems.

CERHR believes the timing is right to evaluate this literature and provide some clarity/interpretation of the published studies both within and across chemicals. The evaluation will consider the consistency of the effects reported in human and experimental animal studies, the relevance of animal models and endpoints for human health, and the biological plausibility of the human and/or experimental animal findings in light of mechanistic and *in vitro* findings. Timing the evaluation to correspond to a key period of growth in the literature is considered particularly advantageous, and intended at this relatively early stage to provide direction for future research and maximize the efficient use of resources.

Proposed Approach:
CERHR will convene a panel of external scientists to evaluate the literature. Specifically, the panel will be asked to address the following two charges:

Charge 1: Provide interpretations of the existing literature, primarily focusing on strength and consistency of findings reported in humans and experimental animals within and

[1] "Born to be Big: Early Exposure to Common Chemicals may be Programming Kids to be Fat" (Newsweek, published September 11, 2009; available at http://www.newsweek.com/id/215179)

across chemicals; strengths/weaknesses and applicability of the animal and *in vitro* models used for human health; and biological plausibility of the reported effects.

Charge 2: Identify data gaps and area for future research.

The evaluation will occur in two steps: (1) preparation of a literature review, and (2) convening a public workshop to develop the overall conclusions and identify research needs. A workshop report will be prepared following the meeting.

Literature Review

As background for the evaluation, CERHR staff will prepare a review of the primary literature in humans and experimental animals. The literature review will also include relevant supporting studies, i.e., *in vitro* or mechanistic data. Prior to the public workshop, groups of the external scientists ("subpanels") will provide assessments of the literature for a specific chemical exposure, e.g., arsenic, PCBs, BPA, etc. This literature review document will be released for public comment before the workshop.

Workshop

In addition to subpanel members, the workshop will include other invited participants and be open to the public. At the workshop, the subpanels will meet, revise their chapter as needed, and develop the overall conclusions outlined in charge 1. These conclusions will be considered in a second round of subpanel sessions designed to identify critical data gaps and research needs (charge 2). The provisional format for the proposed workshop is:

- Phase 1
    - Introductory plenary session
    - Public comments
    - Subpanel sessions to develop the weight of evidence conclusions
- Phase 2
    - Presentation of subpanel findings in plenary session
    - Group discussion of subpanel findings
    - Subpanel sessions to identify data gaps and develop research needs and strategies
- Phase 3
    - Presentation of subpanel recommendations on research needs and strategies in plenary session
    - Group discussion of research recommendations
    - Open general discussion

Following the meeting, a workshop report will be prepared.

Significance and Expected Outcomes:
The significance of the workshop is that it will result in a critical assessment of an emerging issue in environmental health sciences. Expected outcomes depend on the findings of the panel members and workshop discussion, but the overall goal is to

provide some clarity on how to interpret the existing literature. For example, many epidemiological studies have been published on certain exposures, such as PCBs or arsenic, and panel members would be expected to reach conclusions on the consistency of the reported findings. Panel members would also be expected to evaluate the effects across chemicals and potentially reach broader conclusions for general mechanisms, modes of action, or the lack thereof. Other conclusions may relate to the relevance of the animal models used for understanding potential human health impacts. Another level of interpretation would be to consider the human and/or experimental animal findings in the context of biological plausibly given the results of mechanistic or *in vitro* data. The workshop is also intended to result in the development of research recommendations.

References:

Boberg, J., et al. (2008). "Impact of diisobutyl phthalate and other PPAR agonists on steroidogenesis and plasma insulin and leptin levels in fetal rats." Toxicology 250(2-3): 75-81.

Chen, J. Q., et al. (2009). "Regulation of energy metabolism pathways by estrogens and estrogenic chemicals and potential implications in obesity associated with increased exposure to endocrine disruptors." Biochim Biophys Acta 1793(7): 1128-43.

Grun, F. and B. Blumberg (2007). "Perturbed nuclear receptor signaling by environmental obesogens as emerging factors in the obesity crisis." Rev Endocr Metab Disord 8(2): 161-71.

Newbold, R. R., et al. (2009). "Environmental estrogens and obesity." Mol Cell Endocrinol 304(1-2): 84-9.